



CANTOX
HEALTH SCIENCES INTERNATIONAL

Consultants in
Human Health,
Toxicology &
Regulatory Affairs



COMMENTS ON THE DRAFT SUBSTANCE PROFILE FOR STYRENE - GENOTOXICITY

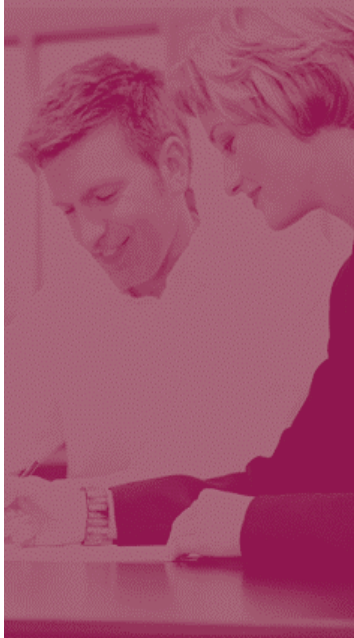


Earle Nestmann, Ph.D.
Cantox Health Sciences International

Board Of Scientific Counselors Meeting
National Toxicology Program
February 24, 2009

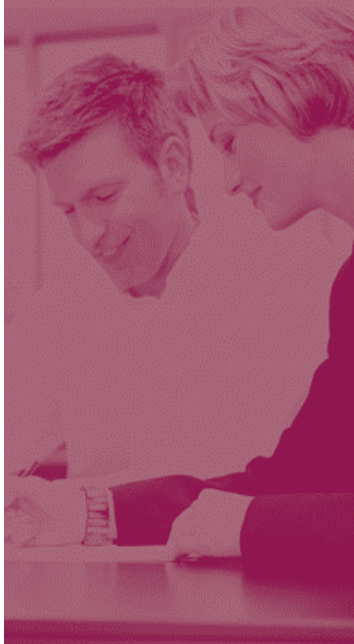


www.cantox.com



COMMENTS ON DRAFT SUBSTANCE PROFILE (DSP) FOR STYRENE

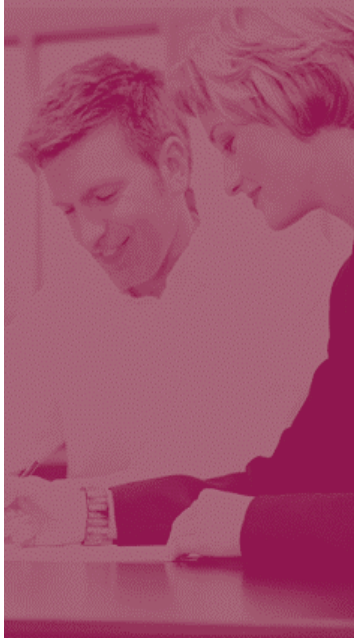
- **General Observations**
- **Metabolism**
- **Specific Comments**
 - *in vitro* genotoxicity
 - *In vivo* genotoxicity
 - Human studies
 - ✓ DNA adduct studies
 - ✓ Cytogenetic damage studies
- **Conclusions**



COMMENTS ON DSP FOR STYRENE

General Observations

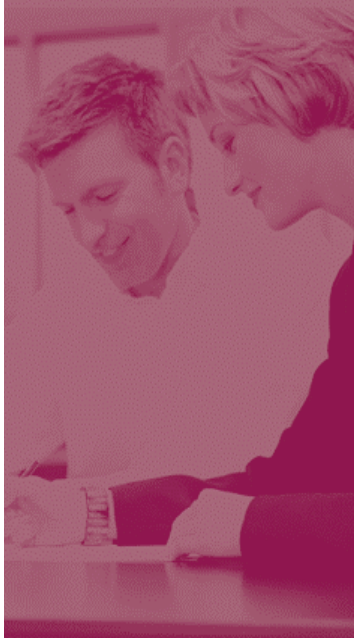
- The DSP and the Background Document summarize genotoxicity studies factually.
- Discussion is biased toward “positive” results (*i.e.*, to support genotoxic effect), ignoring reviews with alternative interpretations.
- There is no meaningful assessment of the genotoxicity data in relation to the metabolism of styrene or to their relevance for assessing the potential human carcinogenicity of styrene.
- The genotoxicity data do not support the listing of styrene in the 12th RoC as “*reasonably anticipated to be a human carcinogen*”.



COMMENTS ON DSP FOR STYRENE

Metabolism

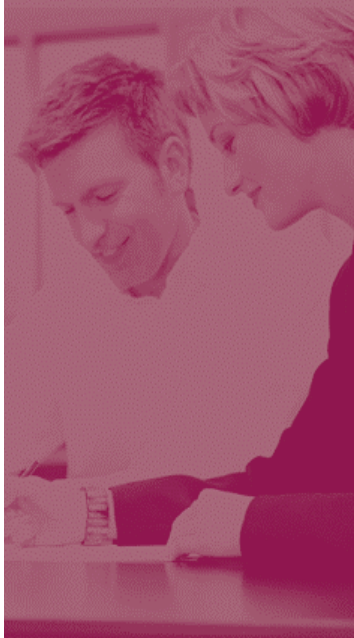
- Styrene can be oxidized by CYP enzymes to styrene-7,8-oxide, a “genotoxic” compound.
- *In vivo*, styrene-7,8-oxide is rapidly detoxified by epoxide hydrolase and glutathione.
- Detoxification mechanisms are not present in *in vitro* assays, hence styrene-7,8-oxide tends to be “positive” in these systems.
- Pharmacokinetic modeling (Sarangapani et al., 2002) shows exposure of lung tissue to styrene-7,8-oxide in humans from inhaled styrene is up to 100-fold and 10-fold lower than in mice and rats, respectively.



COMMENTS ON DSP FOR STYRENE

Specific Comments: *In vitro* Genotoxicity

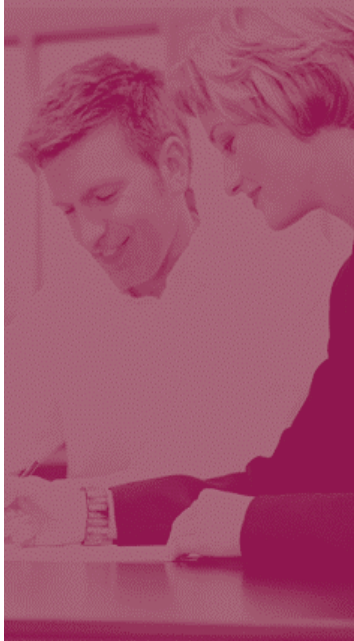
- Results are variable and inconsistent for styrene.
- No consideration of metabolism. Styrene shows activity only under conditions where any styrene oxide formed is not readily detoxified.
- No discussion of the lack of correlation between the results of *in vitro* studies and *in vivo*, worker, or carcinogenicity studies (e.g., DNA adducts in styrene oxide exposed human lymphocytes *in vitro*, but no activity of styrene in mouse micronucleus assays, and no evidence of hematopoietic system cancers in either animals or humans).



COMMENTS ON DSP FOR STYRENE

Specific Comments: *In vivo* Genotoxicity

- Lack of discussion of any negative results (*i.e.*, chromosome aberrations and micronuclei).
- Data considered “positive” actually show inconsistent dose- and temporal-response trends.
- Lack of concordance of the findings of DNA adduct studies in animals *versus* the results of carcinogenicity bioassays is not discussed or acknowledged.

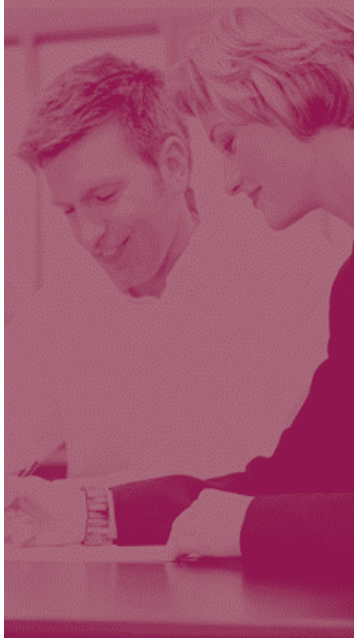


COMMENTS ON DSP FOR STYRENE

Specific Comments: Worker studies

DNA Adducts

- **No interpretive analysis of the findings of DNA adducts reported in styrene-exposed workers.**
- **The biological significance of the types of DNA adducts is not adequately discussed, especially in relation to DNA repair.**
- **DNA adducts indicate exposure not necessarily genetic hazard or risk.**

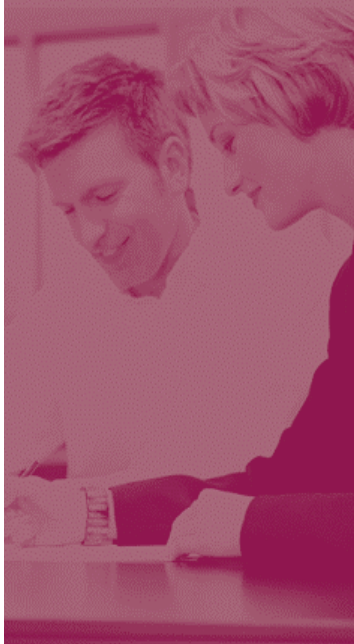


COMMENTS ON DSP FOR STYRENE

Specific Comments: Worker studies

Cytogenetic Damage

- Cytogenetic studies are inconsistent and tend to show results that are contrary to those reported in the *in vivo* animal studies; this is not discussed.
- The inadequacies of the designs (number of subjects, appropriateness of controls, consistency of the data, *etc.*) of many of the cytogenetic studies are not discussed.



COMMENTS ON DSP FOR STYRENE

Conclusions

- The DSP and the background document either present an unbalanced view of the styrene genotoxicity data and/or fail to provide any interpretive analysis with respect to the assessment of the carcinogenic hazard posed by styrene.
- The genetic toxicity data are ambiguous and inconsistent.
- The genotoxicity data do not support the listing of styrene in the 12th RoC.